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PRE-APPEAL BRIEF REQUEST FOR REVIEW

Docket Number (Optional): AC-51-US

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to "Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450" [37 CFR 1.8(a)]

on _____

Signature _____

Typed or printed name _____

Application Number	Filed
10/560,385	01/12/2007

First Named Inventor: Michael G. ORCHARD

Art Unit	Examiner
1625	John MABRY

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

- ☐ applicant/inventor.
- ☐ assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)
- ☑ attorney or agent of record. Registration number 58,337
- ☐ attorney or agent acting under 37 CFR 1.34. Registration number if acting under 37 CFR 1.34 _____

Signature

Brittany LA
Typed or printed name

(973)912-5232
Telephone number

Oct 29, 2010
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☐ *Total of _____ forms are submitted.

REMARKS

Claims 1-4, 6, 7 and 23-38 are pending. Claims 5 and 8-23 were cancelled. Claims 7 and 24-38 were withdrawn. Claims 1-4 and 6[1] have been rejected under 35. U.S.C. § 103(a).

Claims 1-4 are directed to a compound of Formula I and claim 6 is directed to a composition comprising the same. The Examiner maintained the rejection of the claims under § 103(a) as being allegedly obvious in view of WO 02/055498 (hereinafter "WO '498"). The Examiner identified Example 15 on page 26 of WO '498 as the closest art (i.e., the lead compound) based on structural similarity with the claimed compound. The Examiner admitted that "[i]t is not the intention of WO '498 to use compound of Example 15 as a biologically active compound", but argued that "WO '498 removes the protecting groups of similar compounds and tests such compounds for biological activity." *Final Office Action* dated 7/30/2010, p. 4. While recognizing that other compounds of WO '498 are useful for the treatment of various glycolipid storage diseases, the Examiner argued that "Applicant[s] are simply claiming only a compound and that "[the] intended use of such compounds is irrelevant." *Id.* The Examiner, therefore, concluded that WO '498 renders the invention obvious. Applicants respectfully disagree and request reversal of the rejections for the clear errors in the Examiner's analysis.

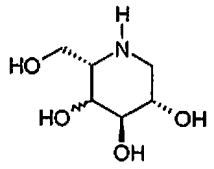
In analyzing obviousness under § 103(a), the Federal Circuit clearly stated in *Eisai Co. LTD v. Dr. Reddy's Laboratories, LTD.*, 533 F.3d 1353 (Fed. Cir. 2008) that "a prima facie case of obviousness for a chemical compound [ ] begins with the reasoned identification of a lead compound." *Id.* at 1359. Also in *Takeda Chemical Industries, LTD v. Alpharm PTY., LTD*, 492 F.3d 1350 (Fed. Cir. 2007), the Court stated that "[i]n addition to structural similarity between the compounds, a prima facie case of obviousness also requires a showing of 'adequate support in the prior art' for the change in structure." *Id.* at 1356. In the recent case *Daiichi Sankyo Co., LTD. v. Matrix Lab. LTD.*, 2010 WL 3504759 (Fed. Cir. 2010), the Court again reiterated that "proving a reason to select a compound as a lead compound depends on more than just structural similarity, but also knowledge in the art of the functional properties and limitations of the prior art compounds. [] Potent and promising activity in the prior art trumps mere structural relationships." *Id.* at *5 (emphasis added). In particular, the Court explained: "it is the possession of promising useful properties in a lead compound that motivates a chemist to make

[1] Claim 23 was also rejected. Applicants cancelled claim 23 in the response dated 9/13/2010. If the amendment has not been entered, Applicants again request cancellation of claim 23, rendering the rejection moot.

structurally similar compounds", warning that "attribution of a compound as a lead compound after the fact must avoid hindsight bias". *Id.*

Here, the Examiner made clear errors by starting the obviousness analysis with the hindsight knowledge of the claimed invention and identifying the compound in the art with THE most similar structure to the claimed compounds as the lead compound in rejecting the claims of the invention. The Examiner also committed clear errors in disregarding the biological activities of the compounds taught in the art when selecting the lead compound, arguing that "[the] intended use of such compounds is irrelevant." *Final Office Action* dated 7/30/2010, page 4. Further, the Examiner committed clear errors in failing to identify any rationale for marking the changes from the prior art compound of Example 15 to the claimed compounds of the invention.

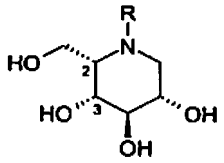
WO '498 exemplified fifteen compounds, fourteen of which are piperidine compounds substituted at the nitrogen ring atom with either an alkyl or unsubstituted phenylalkyl group. Table 2 of WO '498 shows that Examples 2 and 3 (having n-butyl and n-pentyl at the nitrogen ring atom respectively) have an IC_{50} of 10.6μM and 4.0μM, respectively. The only example that discloses a methoxy substituted benzyl R group is Example 15, which is clearly marked as a **"protected intermediate"**. Page 6, lines 21-25 of WO' 498 also teaches that "when P is CH_2Ph the deprotection is conducted in the presence of hydrogen gas and a catalyst such as $PdCl_2$ or palladium on carbon in a suitable solvent . . . It will be understood that when P is CH_2Ph and R is CH_2Ph[,] the R group can also be removed under these conditions". Applicants therefore respectfully submit that when Example 15 is deprotected as described, the resulting compound is a partially de-benzylated or a fully de-benzylated compound, i.e., an unsubstituted 2-hydroxymethyl-3,4,5-piperidinetriol (i.e., Formula II of WO '498):



(II)

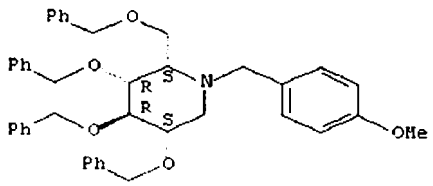
As such, it is clear that Example 15 is useful as an intermediate for the synthesis of various compounds disclosed in WO '498, not the lead compound of the reference.

Comparing Example 15 of WO '498 to the claimed compounds of Formula (I), wherein R is phenylmethyl-, wherein phenyl is substituted by OR^1; and R^1 is C_{4-5} alkyl:



(I)

Formula (I)



Example 15

there are two points of differences: (1) Example 15 has a methoxybenzyl on the ring nitrogen while the currently claimed compounds have a C_{4-5}alkoxyphenylmethyl; and (2) the piperidine ring of Example 15 is substituted with benzyloxy while the currently claimed compounds are substituted with free hydroxy groups. To start from Example 15 of WO '498 and arrive at the compounds of the current invention would therefore require one skilled in the art to take three steps, none of which are taught or suggested in the art so as to render the invention obvious. The first step is to deprotect the compound of Example 15 as WO '498 discloses on page 26, line 20 that Example 15 is a "protected intermediate". Upon obtaining this deprotected compound of Formula II, one skilled in the art would then be required to decide which compound is most likely to succeed (i.e., identify the lead compound). Upon identification of the lead compound, the skilled artisan would finally be required to decide what modifications to make to the existing lead compound so as to arrive at the invention. As argued above, there is no rationale for choosing Example 15 as the lead compound except for hindsight knowledge of the current invention. Further, one skilled in the art would not be motivated to ignore the fourteen examples and make analogs of a "protected intermediate" having no biological properties.

While WO '498 generically discloses the currently claimed compounds, it is established that a disclosure of a generic formula does not by itself render obvious a species of that genus. *See In re Baird*, 16 F.3d 380, 382 (Fed. Cir. 1994) ("The fact that a claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious.")(Citation omitted). Here, nothing in the art suggests that, of all the possible substituents, that the C_{4-5}alkoxybenzyl is preferred. As can be seen, Examples 1 and 2 of the current invention have far superior activities than those in WO '498. Nothing in the art suggests that substituting the piperidine ring with a (C_{4-5}alkoxy)-benzyl in place of the n-butyl or n-pentyl would give a 10-70 fold increase in GCS activities. These properties are clearly unexpected and pursing compounds wherein R is C_{4-5}alkoxybenzyl is clearly unobvious.

The Examiner argued that the intended purpose of the compounds is irrelevant, citing to MPEP §§ 2112-2112.02. MPEP § 2112, however, pertains to rejection based on inherency, stating that "if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present". However, the currently claimed compounds are not identical to Example 15 (neither are they identical to the deprotected compound of Example 15 nor any of the compounds disclosed in WO '498). Significantly, MPEP § 2144.09 states that "if prior art compounds have no utility, or utility only as intermediates, claimed structurally similar compounds may not be *prima facie* obvious over the prior art.". *Id.* In addition, there are numerous cases wherein the Federal Circuit considered utility or properties of prior art compounds (or lack thereof) to be relevant in the determination of non-obviousness. *See In re Lalu*, 747 F.2d 703, 707 (Fed. Cir. 1984) ("a relevant property of a compound cannot be ignored in the determination of non-obviousness"). *See also Ortho-McNeil Pharma., Inc. v. Mylan Lab., Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008) (found nonobviousness where the claimed anti-convulsive compound was synthesized as an intermediate for an antidiabetic drug and wherein "the ordinary artisan in this field would have had to (at the time of invention without any clue of potential utility of the active ingredient) stop at that intermediate and test it for properties far afield from the purpose for the development in the first place (epilepsy rather than diabetes)."). Therefore, Applicants respectfully submit that the difference in utility between Example 15 and the claimed compounds is pertinent to the non-obviousness analysis.

Wherein the Examiner has ignored the biological activities of prior art compounds, used hindsight knowledge of the current invention to select the lead compound and failed to provide rationale for making the changes in the art to arrive at the current invention, the Examiner has committed clear errors. Reconsideration and reversal of the rejections of claims 1-4 and claim 6 are earnestly requested.

Respectfully submitted,

Dated: Oct 29, 2010

By _____

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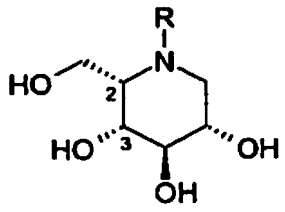
Exhibit A

Listing of the Claims:

1. (Previously presented) 1. A compound of formula (I) in free or pharmaceutically acceptable salt form:



(I)

wherein

R is phenylmethyl-, wherein phenyl is substituted by OR^1; and

R^1 is C_{4-5} alkyl.

2. (Previously presented) The compound as defined in claim 1 wherein the OR^1 substituent on the phenyl is on the 4 position.

3. (Previously presented) The compound of claim 1 being 3,4,5-piperidinetriol, 2-(hydroxymethyl)-1-[(4-pentyloxyphenyl)methyl]-, (2S,3R,4R,5S), in free or pharmaceutically acceptable salt form.

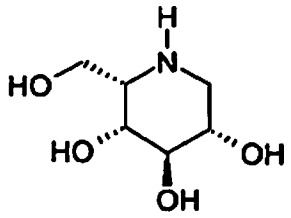
4. (Previously presented) The compound of claim 1 being 3,4,5-piperidinetriol, 1-[(4-butoxyphenyl)methyl]-2-(hydroxymethyl)-, (2S,3R,4R,5S), in free or pharmaceutically acceptable salt form.

5. (Cancelled).

6. (Previously presented) A pharmaceutical composition comprising the compound as defined in claim 1, together with one or more pharmaceutically acceptable carriers, excipients and/or diluents.

7. (Withdrawn–Previously presented) A process for the preparation of the compound as defined in claim 1, which process comprises:

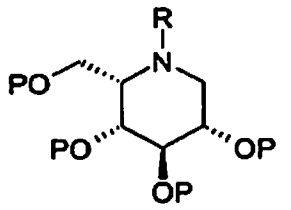
a) reacting a compound of formula (II):



(II)

with an aldehyde of formula R^2CHO, wherein R^2 is phenyl which is substituted as defined in claim 1, using $NaBH_3CN$ or a supported reagent in acetic acid-methanol or HCl-methanol, or using $NaBH(OAc)_3$ in a solvent, or

b) deprotectinq a compound of formula (III):



(III)

wherein R is as defined in claim 1, and P, which may be the same or different, are hydroxy protecting groups.

8-22. (Cancelled).

23. (Cancelled).

24. (Withdrawn–Previously presented) A method for inhibiting glucosylceramide synthase comprising administering to a subject an effective amount of the compound of any one of claims 1 to 4.

25. (Withdrawn–Previously presented) A method for treating a glycolipid storage disease comprising administering to a subject an effective amount of the compound of any one of claims 1 to 4.

26. (Withdrawn–Previously presented) The method of claim 25, wherein the glycolipid storage disease is Gaucher disease, Sandhoffs disease, Tay-Sachs disease, Fabry disease, or GMI gangliosidosis.

27. (Withdrawn–Previously presented) A method for treating Niemann-Pick disease type C, mucopolysaccharidosis type I, mucopolysaccharidosis type IIIA, mucopolysaccharidosis type IIIB, mucopolysaccharidosis type VI or mucopolysaccharidosis type VII, α-mannosidosis, or mucolipidosis type IV, comprising administering to a subject an effective amount of the compound of any one of claims 1 to 4.

28. (Withdrawn–Previously presented) A method for treating cancer in which glycolipid synthesis is abnormal, comprising administering to a subject an effective amount of the compound of any one of claims 1 to 4.

29. (Withdrawn–Previously presented) The method of claim 28, wherein cancer is selected from the group consisting of brain cancer, neuronal cancer, neuroblastoma, renal adenocarcinoma, malignant melanoma, multiple myeloma and multi-drug resistant cancers.

30. (Withdrawn–Previously presented) A method for treating Alzheimer's disease, epilepsy, stroke, Parkinson's disease or spinal injury, comprising administering to a subject an effective amount of the compound of any one of claims 1 to 4.

31. (Withdrawn–Previously presented) A method for treating a disease caused by an infectious microorganism which utilizes glycolipids on a host cell surface as receptors for either the organism itself or for toxins produced by the organism, or an infectious microorganism for which the synthesis of glucosylceramide is essential for its survival, comprising administering to a subject an effective amount of the compound of any one of claims 1 to 4.

32. (Withdrawn–Previously presented) A method for treating a disease associated with abnormal glycolipid synthesis, comprising administering to a subject an effective amount of the compound of any one of claims 1 to 4.

33. (Withdrawn–Previously presented) The method of claim 32, wherein the disease is selected from the group consisting of polycystic kidney disease, diabetic renal hypertrophy and atherosclerosis.

34. (Withdrawn–Previously presented) A method for treating a condition treatable by the administration of a ganglioside, comprising administering to a subject an effective amount of the compound of any one of claims 1 to 4.

35. (Withdrawn–Previously presented) A method for reversibly rendering a male mammal infertile, comprising administering to the male mammal an effective amount of the compound of any one of claims 1 to 4.

36. (Withdrawn–Previously presented) A method for treating obesity, comprising administering to a subject an effective amount of the compound of any one of claims 1 to 4.

37. (Withdrawn–Previously presented) A method for treating an inflammatory disease or disorder associated with macrophage recruitment and activation, comprising administering to a subject an effective amount of the compound of any one of claims 1 to 4.

38. (Withdrawn–Previously presented) The method of claim 37, wherein the disease or disorder is selected from the group consisting of rheumatoid arthritis, Crohn's disease, asthma or sepsis.